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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/055,245	01/22/2002	Mitchell W. Mutz	7610-0001.22	9216
23980	7590	12/02/2003	EXAMINER	
REED & EBERLE LLP 800 MENLO AVENUE, SUITE 210 MENLO PARK, CA 94025			GAKH, YELENA G	
			ART UNIT	PAPER NUMBER
			1743	
DATE MAILED: 12/02/2003				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/055,245

Applicant(s)

MUTZ ET AL.

Examiner

Yelena G. Gakh, Ph.D.

Art Unit

1743

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 January 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-150 is/are pending in the application.
- 4a) Of the above claim(s) 130-150 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-129 is/are rejected.
- 7) ☒ Claim(s) 66 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 January 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.5 6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:
 - I. Claims 1-129, drawn to a method for generation of a small fluid volume, classified in class 436, subclass 86.
 - II. Claims 130-143, drawn to a spatial array comprising a plurality of small fluid volumes, classified in class 422, subclass 35.
 - III. Claims 144-150, drawn to a method for detecting crystals in a fluid, classified in class 436, subclass 86.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the product (the array) can be made by any method of deposition small fluid volumes, which does not comprise acoustic deposition.

Inventions II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions and different effects. Invention II concerns an array of small fluid volumes comprising chemicals and having specific densities of the sites; invention III related to a method utilizing acoustic energy for detecting crystals.

Inventions I and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different modes of operation and different effects. Invention I recites a method of generation of a small fluid volume using acoustic energy, while invention III recites a method utilizing acoustic energy for *detecting* crystals.

Art Unit: 1743

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

2. During a telephone conversation with Louis L. Wu on 11/25/03 a provisional election was made with traverse to prosecute the invention of I, claims 1-129. Affirmation of this election must be made by applicant in replying to this Office action. Claims 130-150 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Double Patenting

3. Claim 66 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 46. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Art Unit: 1743

5. Claims 1-129 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 43 and 78 recite "generation of a small fluid volume". The term "small" in the claims is a relative term, which renders the claim indefinite. The term "small" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 90 recites the limitation "the nucleic acid". There is insufficient antecedent basis for this limitation in the claim, since no "nucleic acid" is recited in parent claim 88. Moreover, it is not clear, what the limitation "the nucleic acid has a conformation" means. Any nucleic acid has "a conformation", and therefore it is not clear, what such limitation defines.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

Art Unit: 1743

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. **Claims 1-37, 41-45, 47-65, 67-72, 75-106, 109-126 and 128-129** are rejected under 35 U.S.C. 103(a) as being unpatentable over Santarsiero et al. (US 6,296,673 B1) in view of Hadimioglu et al. (US 5,565,113) and Hey et al. (Proceedings).

Santarsiero teaches methods and apparatus "for performing array microcrystallizations to determine suitable crystallization conditions for a molecule. The method comprises forming an array of microcrystallizations, each microcrystallization comprising a drop containing a molecule to be crystallized, the drop having a volume of less than 1 μ L; storing the array of microcrystallizations under conditions suitable for molecule crystals to form in the drops in the array; and detecting molecule crystal formation in the drops" (Abstract). "The molecule is preferably a macromolecule such as a protein but may also be other types of macromolecules. The molecule preferably has a molecular weight of at least 500 Daltons, more preferably at least 1000 Daltons, although smaller molecular weight molecules may also be crystallized. In one embodiment, the method comprises: forming an array of microcrystallizations, each microcrystallization including a drop containing a molecule to be crystallized and a mother liquor solution whose composition varies within the array, the drop having a volume of less than 1 μ L; storing the array of microcrystallizations under conditions suitable for molecule crystals to form in the drops in the array; and detecting molecule crystal formation in the drops" (col. 2, lines 34-47). Varying compositions comprise salts, detergents, saccharides, etc. (Figure 9). Varying conditions comprise pH (Figure 2, col. 10, lines 50-60). Varying composition of the mother liquor solution and such conditions as pH inherently leads to a range of protein structures, from fully native protein domain, through partially native and partially denatured protein domain, to fully denatured protein domain. Santarsiero emphasizes, "applicants believe that the rate of crystallization is dependent on the drop volume where crystals form faster when smaller drop volumes are used. As a result, crystals can be formed more rapidly by using the smaller drop volumes used in the present invention. This significantly increases the through-put rate of the method for determining crystallization conditions" (col. 7, lines 22-27).

Although Santarsiero does not specifically indicate temperature and pressure control at ambient conditions, it is obvious to assume that these conditions are controlled, since no varying temperature and pressure is mentioned in the specification, and temperature is listed as one of the factors influencing the process of growing crystals (see col. 2, lines 4-11). It is well recognized in the art that pressure is another factor defining the rate of crystallization, and therefore it would have been obvious to keep both temperature and pressure at ambient conditions.

Santarsiero discloses deposition of "less than 1 μL " volume drops with fluid ejectors comprising pipettes. He fails to disclose acoustic deposition of the material.

Hadimioglu discloses "lithographically defined ejection units" (Title) employing acoustic deposition. He specifically emphasizes, "it should be noted that since acoustically ejected droplets have very small, but accurately controlled, volumes, that acoustic droplet ejectors are particularly useful for depositing proteins".

It would have been obvious for anyone of ordinary skill in the art to modify Santarsiero's method by employing Hadimioglu's acoustic deposition of very small droplets, because Santarsiero specifically indicates that the smaller the volume of the droplets, the more efficient is high throughput screening of crystallization parameters for biological molecules, including proteins (as well as nucleic acids, see col.1), and Hadimioglu emphasizes that obtaining "very small, but accurately controlled, volumes" of the droplets makes the acoustic ejection "particularly useful for depositing proteins". Although Hadimioglu does not specifically indicate the volume of acoustically formed drops, such volumes are known to range from pico- to nanoliters, as specified by Hey, see Abstract.

10. **Claims 38-40, 46, 66, 73-74, 107-108 and 127** are rejected under 35 U.S.C. 103(a) as being unpatentable over Santarsiero in view of Hadimioglu and Hey, as applied to claims 1-37, 41-45, 47-65, 67-72, 75-106, 109-126 and 128-129 above, and further in view of Lube et al. (J. Cryst. Growth) or Subramanian et al. (IEEE Electron Dev. Lett.).

Santarsiero in view of Hadimioglu and Hey do not particularly disclose acoustic detection of crystals.

Lube or Subramanian disclose acoustic detection of crystals: "this phenomenon has been used to extend the acoustic sensor to crystallinity tracking. It has been determined that the

Art Unit: 1743

sensor is sensitive enough to detect the onset of crystallization before any peaks are visible on X-ray diffraction spectra" (Subramanian, page 379, left column).

It would have been obvious for anyone of ordinary skill in the art to use acoustic detection in Santarsiero-Hadimioglu-Hey's method, because Lube or Subramanian demonstrate that this method is more sensitive than conventional X-ray crystallography.

Although none of the references cited above teach fluid volume containing polyethylene glycol (PEG) and DMSO, it would have been obvious for anyone of ordinary skill in the art to screen crystallization of biologically active proteins in DMSO-PEG system, because bioavailability of the active compounds is defined by the degree of their crystallization in pharmaceutical compositions, with DMSO being a conventional solvent for proteins, and polyethylene glycol being a conventional matrix in pharmaceutical compositions.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (703) 306-5906. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (703) 308-4037. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.



Yelena G. Gakh
11/27/03